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E T U O I K E U S T O D I S T U S
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NEW COMPOUNDS

Technical field

The present invention relates to therapeutically active compounds and pharmaceutically acceptable salts and esters thereof useful in the treatment of nuclear receptor, especially steroid receptor, and in particular androgen receptor (AR) dependent conditions, and to pharmaceutical compositions containing such compounds. In particular, the invention discloses novel non-steroidal propionanilide structured compounds having utility as tissue-selective androgen receptor modulators (SARM). The compounds of the invention, which possess AR agonist activity, are useful in hormonal therapy, especially in treatment or prevention of conditions like male hypogonadism and age-related conditions such as andropause.

Background of the invention

Nuclear hormone receptors make up a family of ligand-inducible trancription factors whose members are involved in multiple physiological and developmental functions. During the last 20 years, more than sixty structurally and functionally related proteins belonging to this family have been identified. Nuclear hormone receptor family includes, in addition to classical steroid receptors (estrogen receptor, progesterone receptor, androgen receptor, glucocorticoid receptor and mineralo-corticoid receptor) also receptors e.g. for thyroid hormone, vitamin D and retinoids. Furthermore, a subclass of so-called orphan receptors for which no ligands have been identified up to date belong to this protein family. See Mangelsdorf et al, Cell (1995) 83(6): 835-839 and references therein. There exists an intense research directed to identify novel modulators for these proteins, ultimate goal thus being to find new therapies and treatment options for conditions and diseases modulated by nuclear/steroid receptors.

Steroidal androgens have been used for decades in the treatment of diseases resulting from deficiency in androgen action. They have also received attention for their use as hormone replacement therapy of aging men and in regulation of male fertility. However, current steroidal androgens, such as synthesized testosterone and its derivatives, have severe limitations. Testosterone is rapidly degraded by the liver

and thus has a low systemic bioavailability after oral administration. Further, orally available testosterone formulations, e.g. methyltestosterone, have been associated with alterations in liver function. Various other attempts have been made to overcome these drawbacks of steroidal androgens as therapeutic agents, but with limited success. Current testosterone formulations used in clinical practise include e.g. injections, patches and gels.

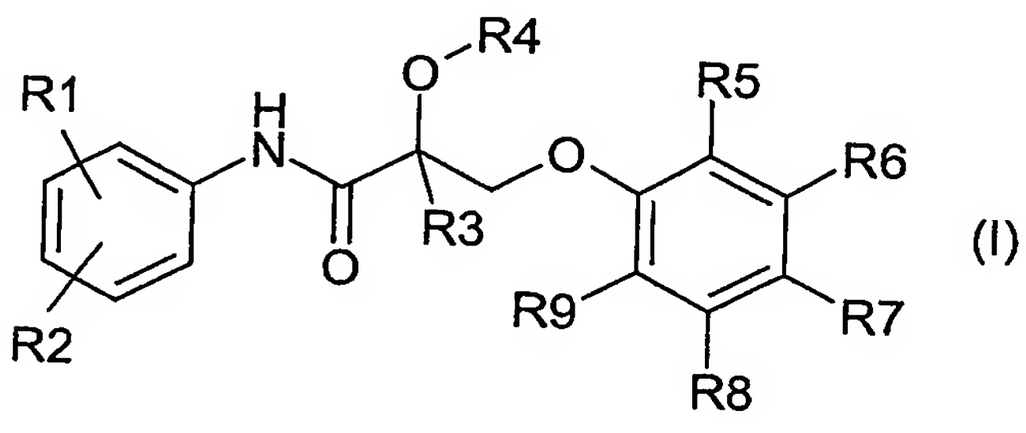
In recent years, there have been growing interest in the development of nonsteroidal modulators for steroid receptors for therapeutical use. It has been shown that nonsteroidal ligands can achieve better receptor selectivity and better physicochemical, pharmacokinetic and pharmacological properties. For androgen receptor (AR), nonsteroidal antagonists (antiandrogens) are now used clinically to counteract the undesirable actions of excessive androgens. In contrast, nonsteroidal AR agonists, which would have potential in the treatment of diseases resulting from androgen deficiency, have just recently been reported. Still, the structural elements of nonsteroidal ligands that would lead to optimal agonist activity and tissue selectivity are poorly defined.

Non-steroidal propionanilides having androgen receptor modulating activity have been described e.g. in patent publications EP 100172, EP 253503, WO 98/53826 and WO 02/16310. The design of propionanilide structured AR modulators has concentrated on compounds where the anilide ring is substituted by two electron-withdrawing substituents such as halogen, cyano, trifluoromethyl or nitro, since such substitution has been reported to enhance the androgen receptor binding affinity of the ligand. See e.g. Tucker, H. et al., J. Med. Chem., 1988, 31, 954-959.

Summary of the invention

It has now been found that compounds of formula (I) are potent nuclear receptor modulators, in particular androgen receptor modulators. In particular, the compounds of formula (I) possess utility as tissue-selective androgen receptor modulators (SARM). Compounds of formula (I), which possess AR agonist activity, have been found to be particularly suitable for use in hormonal therapy, especially in the treatment or prevention of conditions like male hypogonadism and age-related conditions such as andropause, e.g. for providing tissue-selective androgenic or anabolic effects.

The compounds of the present invention have a structure represented by formula (I)



(I)

wherein

R_1 is $(C_1\text{-}C_7)$alkyl;

R_2 is nitro, cyano or halogen;

R_3 is hydrogen, $(C_1\text{-}C_7)$alkyl or halo$(C_1\text{-}C_7)$alkyl;

R_4 is hydrogen, $(C_1\text{-}C_7)$alkyl, COR_{10} or SO_2R_{13};

R_5, R_6, R_7, R_8 and R_9 are independently hydrogen, halogen, nitro, cyano, $(C_1\text{-}C_7)$alkyl, halo$(C_1\text{-}C_7)$alkyl, cyano$(C_1\text{-}C_7)$alkyl, amino, mono- or di$(C_1\text{-}C_7)$alkyl-amino, amino$(C_1\text{-}C_7)$alkyl, hydroxy$(C_1\text{-}C_7)$alkyl, $-NHCOR_{10}$, $-N(COR_{10})_2$, $-COR_{11}$, $-OR_{12}$, OSO_2R_{13}, SO_2R_{14} or SR_{15} or an imide ring; or R_5 and R_6, R_6 and R_7, R_7 and R_8, or R_8 and R_9 form, together with any of the ring atom(s) to which they are attached, a condensed 5 to 7 membered aliphatic or aromatic carbocyclic ring or a condensed 5 to 7 membered heterocyclic ring containing 1 to 3 heteroatom(s) selected from N, O and S;

R_{10} and R_{11} are independently $(C_1\text{-}C_7)$alkyl, $(C_2\text{-}C_7)$alkenyl, halo$(C_1\text{-}C_7)$alkyl, $(C_6\text{-}C_{10})$aryl, $-N(R_{16})_2$ or $-OR_{17}$;

R_{12} and R_{15} are independently hydrogen, $(C_1\text{-}C_7)$alkyl, $(C_2\text{-}C_7)$alkenyl, halo$(C_1\text{-}C_7)$alkyl, amino$(C_1\text{-}C_7)$alkyl, mono- or di$(C_1\text{-}C_7)$alkylamino$(C_1\text{-}C_7)$alkyl, $(C_6\text{-}C_{10})$aryl, $-COR_{18}$;

R_{13} and R_{14} are independently $(C_1\text{-}C_7)$alkyl or $(C_2\text{-}C_7)$alkenyl, halo$(C_1\text{-}C_7)$alkyl or $(C_6\text{-}C_{10})$aryl;

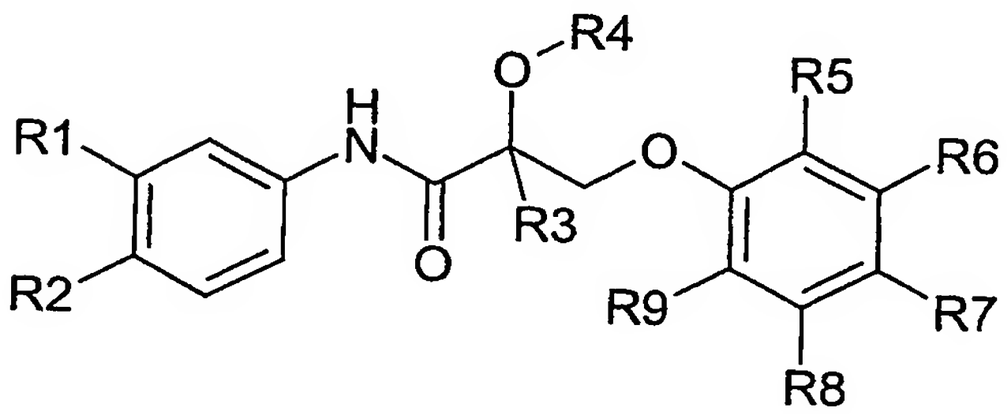
R_{16} and R_{17} are independently hydrogen, $(C_1\text{-}C_7)$alkyl, $(C_2\text{-}C_7)$alkenyl, halo$(C_1\text{-}C_7)$alkyl , amino$(C_1\text{-}C_7)$alkyl or $(C_6\text{-}C_{10})$aryl;

R_{18} is $(C_1\text{-}C_7)$alkyl, $(C_2\text{-}C_7)$alkenyl, halo$(C_1\text{-}C_7)$alkyl or $(C_6\text{-}C_{10})$aryl;

and wherein each aryl or ring residue defined above may be substituted;

and pharmaceutically acceptable salts and esters thereof.

In one class of preferred compounds are compounds of formula (Ib), wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8 and R_9 are as defined above.



(Ib)

In another class of preferred compounds are compounds of formula (I) or (Ib), wherein R_1 is methyl and R_2 is nitro. In another class of preferred compounds are compounds of formula (I) or (Ib) wherein R_4 is hydrogen and R_3 is methyl. In another class of preferred compounds are compounds of formula (I) or (Ib) wherein R_5, R_6, R_7, R_8 and R_9 are independently hydrogen, halogen, cyano, (C_1-C_7)alkyl, (C_1-C_7)alkoxy, halo(C_1-C_7)alkyl, hydroxy(C_1-C_7)alkyl or -$NHCOR_{10}$, wherein R_{10} is (C_1-C_7)alkyl or halo(C_1-C_7)alkyl. Particularly preferred are compounds of formula (I) or (Ib) wherein at least one of R_5, R_6, R_7, R_8 and R_9 is a halogen, preferably fluorine. Most preferably R_7 is a halogen, preferably fluorine.

The present invention provides further a method of hormonal therapy, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of formula (I).

The present invention provides further a method for the treatment or prevention of androgen receptor (AR) dependent conditions, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of formula (I).

The present invention provides further a method the treatment or prevention of androgen deficiency, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of formula (I).

The present invention provides further a method the treatment or prevention of male hypogonadism and age-related conditions such as andropause, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of formula (I).

The present invention also relates to a method of hormonal therapy, e.g. the treatment or prevention of androgen deficiency, comprising oral administration of compound of formula (I).

The present invention also provides a pharmaceutical composition comprising a compound of formula (I) together with a pharmaceutically acceptable carrier.

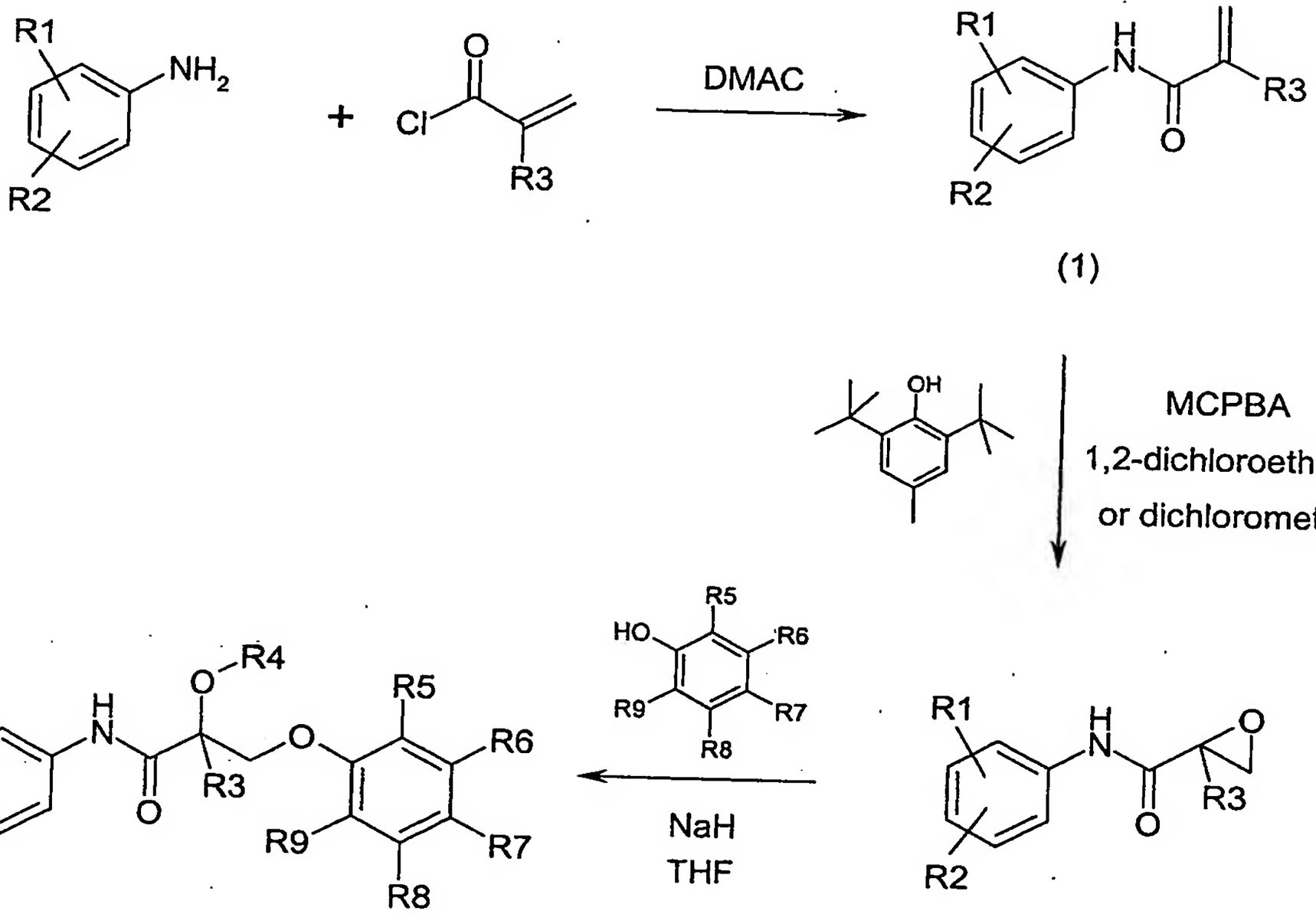
Brief Description of the Drawings

FIG. 1 shows the androgenic and anabolic activity of a compound of the invention in *levator ani* -muscle, seminal vesicle and ventral prostate of immature male Spraque Dawley rat.

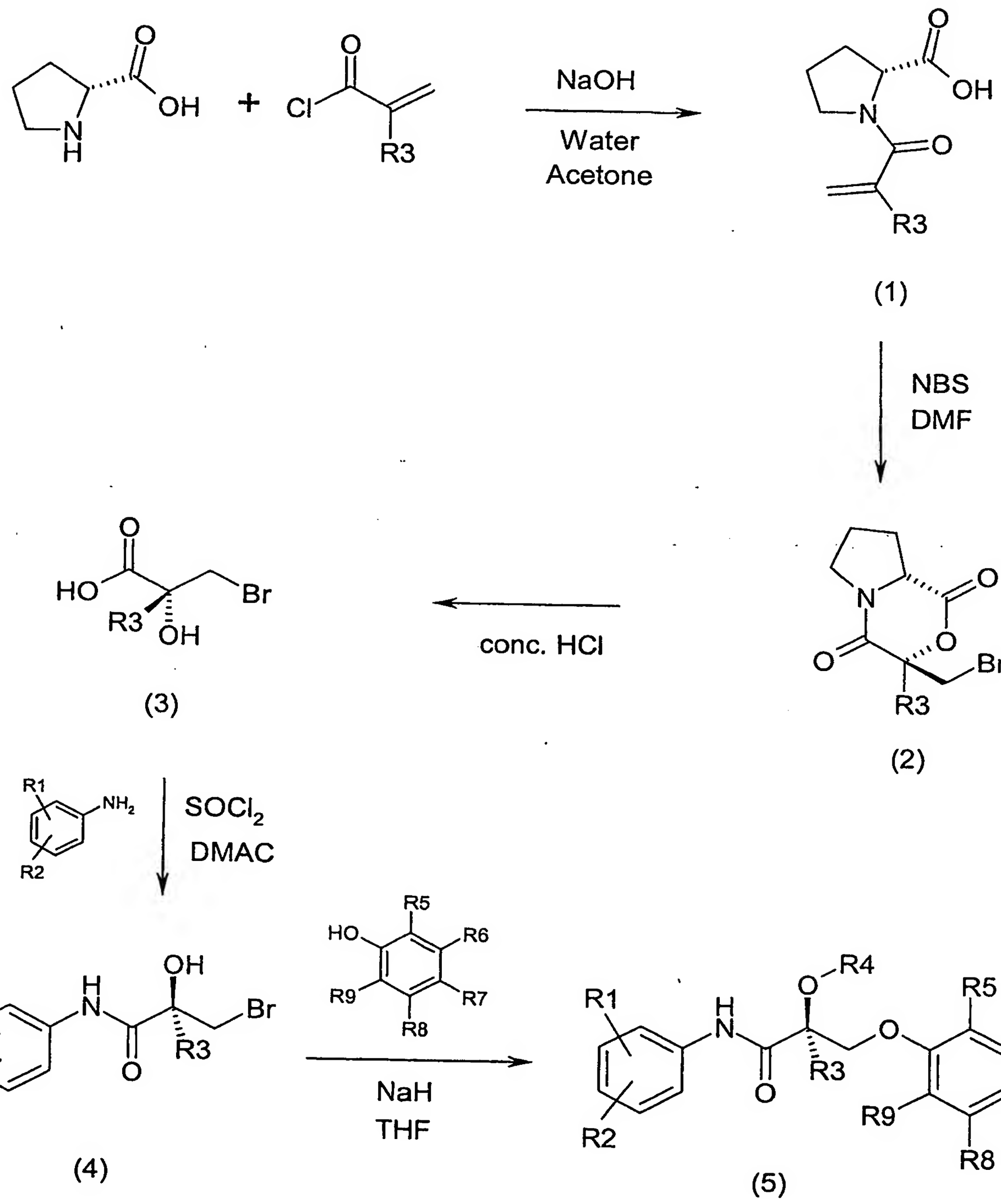
Detailed description of the invention

The compounds of the invention can be prepared by a variety of synthetic routes analogously to the methods known in the literature using suitable starting materials. In particular, the compounds of the invention can be prepared analogously to the general methods described in WO 98/53826. For example, the compounds of the invention can be prepared e.g. analogously or according to the reaction Scheme 1 or 2:

Scheme 1 (Method A)



Scheme 2 (Method B)



Pharmaceutically acceptable salts, e.g. acid addition salts with both organic and inorganic acids are well known in the field of pharmaceuticals. Non-limiting examples of these salts include chlorides, bromides, sulfates, nitrates, phosphates, sulfonates, formates, tartrates, maleates, citrates, benzoates, salicylates and ascorbates. Pharmaceutically acceptable esters, when applicable, may be prepared by known methods using pharmaceutically acceptable acids that are conventional in the field of pharmaceuticals and that retain the pharmacological properties of the free form. Non-limiting examples of these esters include esters of aliphatic or aromatic alcohols, e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *sec*-butyl, *tert*-butyl esters. Phosphate esters and carbonate esters, are also within the scope of the invention.

The terms employed herein have the following meanings:

The term "halo" or "halogen", as employed herein as such or as part of another group, refers to chlorine, bromine, fluorine or iodine.

The term "(C_1-C_7)alkyl", as employed herein as such or as part of another group, refers to a straight, branched or cyclized chain radical having 1 to 7 carbon atoms. Representative examples of (C_1-C_7)alkyl include, but are not limited to, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *tert*-butyl, *n*-pentyl, isopentyl, neopentyl, *n*-hexyl, cyclopentyl, cyclohexyl and the like.

The term "(C_2-C_7)alkenyl", as employed herein as such or as part of another group, refers to a straight, branched or cyclized chain radical having 2 to 7 carbon atoms, and containing (a) double bond(s).

The term "hydroxy", as employed herein as such or as part of another group, refers to an –OH group.

The term "hydroxy(C_1-C_7)alkyl", as employed herein, refers to at least one hydroxy group, as defined herein, appended to the parent molecular moiety through an (C_1-C_7)alkyl group, as defined herein. Representative examples of hydroxy(C_1-C_7)alkyl include, but are not limited to, hydroxymethyl, 2,2-dihydroxyethyl, 1-hydroxyethyl, 3-hydroxypropyl, 1-hydroxypropyl, 1-methyl-1-hydroxyethyl, 1-methyl-1-hydroxypropyl, and the like.

The term "halo(C_1-C_7)alkyl", as employed herein, refers to at least one halogen, as defined herein, appended to the parent molecular moiety through an (C_1-C_7)alkyl group, as defined herein. Representative examples of halo(C_1-C_7)alkyl include, but are not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, 2-chloroethyl, 3-bromopropyl, and the like.

The term "cyano", as employed herein as such or as part of another group, refers to a –CN group.

The term "cyano(C_1-C_7)alkyl", as employed herein, refers to a cyano group, as defined herein, appended to the parent molecular moiety through an (C_1-C_7)alkyl group, as defined herein. Representative examples of cyano(C_1-C_7)alkyl include, but are not limited to, cyanomethyl, 1-cyanoethyl, 1-cyanopropyl, 2-cyanopropyl, and the like.

The term "amino", as employed herein as such or as part of another group, refers to a $–NH_2$ group.

The term "amino(C_1-C_7)alkyl", as employed herein, refers to at least one amino group, as defined herein, appended to the parent molecular moiety through an (C_1-C_7)alkyl group, as defined herein. Representative examples of amino(C_1-C_7)alkyl include, but are not limited to, aminomethyl, 2-aminoethyl, 1-aminoethyl, 2,2-diaminoethyl, 3-aminopropyl, 2-aminopropyl, 4-aminobutyl, 1-methyl-1-aminoethyl, and the like.

The term "mono- or di(C_1-C_7)alkylamino", as employed herein as such or as part of another group, refers to one or two (C_1-C_7)alkyl group(s), as defined herein, appended to the parent molecular moiety through an amino group, as defined herein. Representative examples of mono- or di(C_1-C_7)alkylamino include, but are not limited to methylamino, ethylamino, propylamino, butylamino, dimethylamino, diethylamino, *N*-ethyl-*N*-methylamino, and the like.

The term "mono- or di(C_1-C_7)alkylamino(C_1-C_7)alkyl", as employed herein, refers to a mono- or di(C_1-C_7)alkylamino group, as defined herein, appended to the parent molecular moiety through a (C_1-C_7)alkyl group, as defined herein.

Representative examples of mono- or di(C_1-C_7)alkylamino(C_1-C_7)alkyl include, but are not limited to, *N*,*N*-dimethylaminomethyl, *N*,*N*-diethylaminomethyl, *N*-methylaminoethyl, *N*-methylaminopropyl, *N*-ethyl-*N*-methylaminomethyl, and the like.

The term "(C_1-C_7)alkoxy", as employed herein as such or as part of another group, refers to -O-(C_1-C_7)alkyl, wherein -(C_1-C_7)alkyl is as defined herein. Representative examples of (C_1-C_7)alkoxy include, but are not limited to methoxy, ethoxy, propoxy, butoxy, isobutoxy, *sec*-butoxy, *tert*-butoxy, and the like.

The term "(C_1-C_7)alkoxy(C_1-C_7)alkyl", as employed herein, refers to at least one (C_1-C_7)alkoxy group, as defined herein, appended to the parent molecular moiety through an (C_1-C_7)alkyl group, as defined herein. Representative examples of (C_1-C_7)alkoxy(C_1-C_7)alkyl include, but are not limited to methoxymethyl, ethoxymethyl, 2-methoxyethyl, 2-ethoxyethyl, 3,3-dimethoxypropyl, 2,4-dimethoxybutyl and the like.

The term "(C_6-C_{10})aryl" as employed herein by itself or as part of another group refers to a monocyclic or bicyclic group containing 6 to 10 carbon atoms in the ring portion. Representative examples of (C_6-C_{10})aryl include, but are not limited to phenyl, naphtyl and the like.

The term "(C_2-C_7)acyl" as employed herein by itself or as part of another group refers to alkylcarbonyl or alkenylcarbonyl group having 2 to 7 carbon atoms, and examples thereof include acetyl, propanoyl, isopropanoyl, butanoyl, *sec*-butanoyl, *tert*-butanoyl and pentanoyl.

The term "substituted" as used herein in connection with various residues refers to halogen substituents, such as fluorine, chlorine, bromine, iodine, or (C_1-C_7)alkyl, halo(C_1-C_7)alkyl, hydroxy, amino, (C_1-C_7)alkoxy, (C_2-C_7)acyl (C_1-C_7)alkylamino, amino(C_1-C_7)alkyl, nitro, cyano, or thiol substituents.

The "substituted" groups may contain 1 to 3, preferably 1 or 2, most preferably 1 of the above mentioned substituents.

The definition of formula (I) above is inclusive of all the possible stereoisomers of the compounds, including geometric isomers, e.g. *Z* and *E* isomers (*cis* and *trans* isomers), and optical isomers, e.g. diastereomers and enantiomers, and all prodrugesters, e.g. phosphate esters and carbonate esters. Furthermore, the invention includes in its scope both the individual isomers and any mixtures thereof, e.g. racemic mixtures. The individual isomers may be obtained using the corresponding isomeric forms of the starting material or they may be separated after the preparation of the end compound according to conventional separation methods. For the separation of optical isomers, e.g. enantiomers, from the mixture thereof the conventional resolution methods, e.g. fractional crystallisation, may be used.

Compounds of the invention may be administered to a patient in therapeutically effective amounts which range usually from about 0.1 to about 1000 mg per day depending on the age, weight, ethnic group, condition of the patient, condition to be treated, administration route and the androgen (AR) modulator used. The compounds of the invention can be formulated into dosage forms using the principles known in the art. It can be given to a patient as such or in combination with suitable pharmaceutical excipients in the form of tablets, granules, capsules, suppositories, emulsions, suspensions or solutions. Choosing suitable ingredients for the composition is a routine for those of ordinary skill in the art. It is evident that suitable carriers, solvents, gel forming ingredients, dispersion forming ingredients, antioxidants, colours, sweeteners, wetting compounds and other ingredients normally used in this field of technology may be also used. The compositions containing the active compound can be given enterally or parenterally, the oral route being the preferred way. The contents of the active compound in the composition is from about 0.5 to 100 %, preferably from about 0.5 to about 20 %, per weight of the total composition.

The present invention will be explained in more detail by the following examples. The examples are meant only for illustrating purposes and do not limit the scope of the invention defined in claims.

EXPERIMENTS

Experiment 1. AR Binding Assay

Ventral prostates were obtained form rats castrated 24 h prior to sacrifice. Fresh prostate was minced and washed with Buffer A (Schilling and Liao, Prostate, 5:581-588, 1984). The minces were then homogenized in 3 x volume of Buffer A containing protease inhibitors (Complete, Mini, EDTA-free Roche). The homogenate was centrifuged at 30000g for 30 min. The resultant supernatants were treated with 1 x volume of dextran-coated charcoal solution (12,5 g activated charcoal, 12,5 g dextran per liter of buffer A) to remove endogenous steroids. The samples were incubated for 5 min and centrifuged at 16000g for 10 min. Aliquots of the charcoal-treated cytosol were taken for androgen receptor assays. All procedures were carried out at 0-4°C.

Cytosol androgen receptor concentration was determined as described (Isomaa et al., Endocrinology, 111: 833-843, 1982) with minor modifications. Cytosol preparations were prepared as described above, and bound and free steroids were separated by treatment with an equal volume of dextran-charcoal suspension for 5 min at 4°C followed by centrifugation at 16000g for 10 min. Bound radioactivity was determined by counting supernatant fractions in 1 ml of OptiPhase HiSafe3 (PerkinElmer).

Cytosol preparations were labelled with 1 nM [^{3}H]-mibolerone overnight at 0°C (total). To determine AR binding activity of the compounds of the present invention (test compounds), the ability of test compounds to compete with [^{3}H]7α,17α-dimethyl-17β-hydroxy-4-estren-3-one ([^{3}H]-mibolerone) binding was studied. 1 nM [^{3}H]-mibolerone and test compounds in two concentrations (0,2 and 2 uM) were incubated overnight at 0°C. To determine non-specific binding, parallel incubations were carried out using 1 nM concentration [^{3}H]-mibolerone with 500-fold molar excess of unlabelled testosterone. Two replicates were used for each sample. After incubation, bound and free steroids were separated as described above and bound radioactivity was determined. The ability of the test compounds to bind AR is reported as reduction in bound radioactivity obtained with 1 nM [^{3}H]-mibolerone. The results are shown in Table 1. The results (% inhibition) were calculated as: % inhibition = $100 - (100x(average_{test\ compound}/average_{total}))$.

Table 1. AR binding assay. Inhibition (%) of [3H]-mibolerone binding.

Compound of Example No.	Inhibition (%) of [3H]-mibolerone binding at 0.2 μM	Inhibition (%) of [3H]-mibolerone binding at 2.0 μM
1.	91	101
3.	103	115
11.	98	105
12.	77	101
39.	77	96
2.	93	100
13.	77	90
15.	46	77
16.	50	91
17.	95	98
14.	75	95
18.	90	99
26.	62	92
5.	25	74
6.	68	95
19.	83	99
20.	13	83
7.	74	98
4.	90	88
8.	93	109
28.	90	88
24.	75	93
23.	88	92
36.	3	50
9.	41	102
10.	5	83
25.	96	98
27.	34	89
30.	80	99
26.	18	75
29.	92	90
21.	26	91

Experiment 2. AR agonism and antagonism in immature male rats

The title compound of Example 3, abbreviated here as compound A, was further studied in *in vivo* experiment. The agonism and antagonism of the compound with subcutaneous dosing was tested in immature male Spraque Dawley rat 3-day assay by analyzing the relative weights of ventral prostate, seminal vesicle, and *levator ani*-muscle. Testosterone propionate was used as a reference compound.

Testosterone propionate (abbreviated here TP) and compound A were first dissolved into DMSO and then into the vehicle sesame oil. Sprague-Dawley untreated male rats (18-19 days old) weighing about 50 g were used in the experiment. Rats were weighed and randomly distributed into five groups, with 5 animals per group (Table 1). Compound A (doses 2 and 20 mg/kg) and testosterone propionate (dose 5 mg/kg) were given subcutaneously (s.c.) into the neck/back of the animals at a constant volume of 100 microl dosing solution/animal/day. The animals were dosed once daily for three days, and clinical [redacted] were recorded during dosing. At the end of the study, animals were weighed and anaesthetised by CO_2 asphyxiation. Ventral prostate, seminal vesicles, and *levator ani*-muscle were dissected out, chilled, and weighed. For statistical analysis, the weights of all organs were normalized to body weights, and analyzed for statistical significant difference by single-factor ANOVA.

Table 2. Animal groups and experimental design

Dose group & group number	Number of animals
1. Vehicle	5
2. Testosterone propionate (TP) 5mg/kg s.c.	5
3. Compound A, 2 mg/kg	5
4. Compound A, 20 mg/kg	5
5. TP 5 mg/kg + Compound A, 20 mg/kg s.c.	5

The results are shown in Figure 1. Compound A shows androgenic and anabolic activity. The relative weights of ventral prostate, seminal vesicle and *levator ani* -muscle increased significantly with administration of testosterone propionate. Compared with testosterone propionate, compound A showed tissue selectivity. At dose 20 mg/kg it clearly increased the relative weight of *levator ani*-muscle and significantly the relative weight of seminal vesicle, but only minimally the relative

weight of the prostate. Furthermore, compound A showed significant antagonistic activity in seminal vesicle. Neither testosterone propionate nor compound A had any effect on the body weights (data not shown). In the Figure, "a" means agonism, $p<0.01$ compared to vehicle group, "b" means antagonism, $p<0.05$ compared to testosterone group, bars represent mean ± SEM.

EXAMPLES:

Example 1. (Method A)

3-(4-Acetylaminophenoxy)-2-hydroxy-2-methyl-N-(3-methyl-4-nitrophenyl)-propionamide

a) 2-Methyl-N-(3-methyl-4-nitrophenyl)acrylamide

3-Methyl-4-nitroaniline (2.0 g, 13 mmol) in N,N-dimethylacetamide (DMAC) (6 ml) was added dropwise to a cooled solution of methacryloyl chloride (2.0 ml, 20.7 mmol) in a nitrogen atmosphere while the temperature of the reaction mixture was maintained between 0 –5 °C. The solution was allowed to warm to room temperature and the mixture was stirred over night. The mixture was poured into water (70 ml) and extracted with ethyl acetate (4 x 40 ml). The organic phase was washed with saturated Na_2CO_3 (3 x 20 ml) and water (1 x 50 ml), dried over Na_2SO_4 and evaporated. The yield of the crude product was 4.17 g (contains DMA, theoretical yield 2.9 g), and it was used without further purifications. ^{1}H NMR (DMSO-d_6): 1.97 (3H, s), 2.55 (3H, s), 5.62 (1H, m), 5.96 (1H, m), 7.80 (2H, m), 8.05 (1H, m), 10.22 (1H, s).

b) 2-Methyloxirane-2-carboxylic acid (3-methyl-4-nitrophenyl)amide

m-Chloroperoxybenzoic acid (6.7 g, 29.9 mmol) was added in portions at 60 °C to a solution of 2-methyl-N-(3-methyl-4-nitrophenyl)acrylamide and 2,6-di-tert-butyl-4-methylphenol (66 mg) in 1,2-dichloroethane (80 ml). The stirring was continued at 60 °C for 6 h, and the reaction mixture was allowed to cool to the room temperature. The precipitated m-chlorobenzoic acid was filtered, and the filtrate was extracted with 1 M Na_2CO_3 (4 x 60 ml). The organic phase was dried over Na_2SO_4 and evaporated. The yield was 3.05 g. ^{1}H NMR (DMSO-d_6): 1.54 (3H, s), 2.51 (3H,

s), 2.99 (1H, d, J=5.1 Hz), 3.05 (1H, d, J=5.1 Hz), 7.79 (2H, m), 8.01 (1H, m), 9.98 (1H, s).

(c) 3-(4-Acetylaminophenoxy)-2-hydroxy-2-methyl-N-(3-methyl-4-nitrophenyl)propionamide

A solution of 4-acetamidophenol (2.9 g, 19 mmol) in THF (60 ml) was added dropwise to a stirred suspension of sodium hydride (0.46 g, 19 mmol, 60 % dispersion in mineral oil) in THF (60 ml) and the temperature was kept below 5 °C during the addition. The mixture was stirred for 10 min and a solution of 2-methyl-oxirane-2-carboxylic acid (3-methyl-4-nitrophenyl)amide (3.05 g, 13 mmol) in THF (120 ml) was added. The mixture was heated to 60 °C and stirred at this temperature for 7 h, and allowed to cool to the room temperature. The solvent was evaporated and the residue was dissolved to the mixture of water (150 ml) and ethyl acetate (150 ml). The pH was adjusted to 2 - 3 with 2 M HCl and the phases were separated. The aqueous phase was extracted with ethyl acetate (4 x 150 ml). The combined organic phase was washed with 1 M Na_2CO_3 (5 x 100 ml), dried over Na_2SO_4 and evaporated. The oily residue was crystallised from the mixture of ethyl acetate – diethyl ether (10 : 1). The crude product was recrystallised from ethyl acetate. The yield was 2.5 g. ^{1}H NMR (DMSO-d_6): 1.42 (3H, s), 1.99 (3H, s), 2.53 (3H, s), 3.93 (1H, d, J=9.6 Hz), 4.16 (1H, d, J=9.6 Hz), 6.20 (1H, bs), 6.84 (2H, d, J=9.0 Hz), 7.44 (2H, d, J=9.0 Hz), 7.88 (1H, dd, J=9.0 Hz and 2.3 Hz), 7.93 (1H, d, J=2.3 Hz), 8.04 (1H, d, J=9.0 Hz), 9.76 (1H, s), 10.15 (1H, bs).

Example 2.

3-(4-Acetylamino-3-fluorophenoxy)-2-hydroxy-2-methyl-N-(3-methyl-4-nitrophenyl)propionamide

a) N-(2-Fluoro-4-hydroxyphenyl)acetamide

Acetic anhydride (1.3 ml, 13.8 mmol) was added dropwise to a solution of 4-amino-3-fluoro phenol (1.0 g, 7.9 mmol) in acetic acid (25 ml) at room temperature. The reaction mixture was stirred at room temperature for 2 h and water (2 ml) was added and the stirring was continued for 30 minutes at room temperature. The mixture was evaporated to dryness with rotary evaporator. The yield of the crude product was 1.3 g (100 %) and it was used without further purification.

^{1}H NMR (DMSO-d_6): 2.00 (3H, s), 6.50-6.68 (2H, m), 7.39 (1H, m), 9.39 (1H, s), 9.72 (1H, s).

b) 3-(4-Acetylamino-3-fluorophenoxy)-2-hydroxy-2-methyl-N-(3-methyl-4-nitrophenyl)propionamide

The compound was synthesised according to the procedure described in Example 1c. N-(2-Fluoro-4-hydroxyphenyl)acetamide (0.5 g, 3.0 mmol) and 2-methyl-oxirane-2-carboxylic acid (3-methyl-4-nitrophenyl)amide (0.6 g, 2.5 mmol) was used as starting materials. The product was crystallised from the mixture of ethyl acetate and diethyl ether (1:1). The yield was 0.39 g. ^{1}H NMR (DMSO-d_6): 1.42 (3H, s), 2.02 (3H, s), 2.53 (3H, s), 3.97 (1H, d, J=9.7 Hz), 4.21 (1H, d, J=9.7 Hz), 6.23 (1H, bs), 6.72 (1H, m), 6.90 (1H, m), 7.56 (1H, m), 7.88 (1H, dd, J=9.0 Hz and 2.2 Hz), 7.93 (1H, d, J=2.2 Hz), 8.03 (1H, d, J=9.0 Hz), 9.51 (1H, s), 10.15 (1H, bs).

Example 3. (Method B)

(2S)-3-(4-Acetylaminophenoxy)-2-hydroxy-2-methyl-N-(3-methyl-4-nitrophenyl)propionamide

a) (2R)-1-(2-Methylacryloyl)pyrrolidine-2-carboxylic acid

D-proline (5 g, 43.4 mmol) was dissolved in 2 M NaOH (26 ml) and cooled in an ice bath, and the solution was diluted with acetone (26 ml). An acetone solution (26 ml) of methacryloyl chloride (6.3 ml, 65.1 mmol) and a 2 M NaOH solution (34 ml) were simultaneously added over a period of 1h to the solution of D-proline. After addition the resulting mixture was stirred for 3 h at room temperature. The mixture was evaporated at 40 °C, extracted with ether (2 x 40 ml) and acidified to pH 2 with concentrated HCl. The resulting mixture was extracted with ethyl acetate (3 x 50 ml), dried over Na_2SO_4 and evaporated. The yield was 11.5 g (theoretical 8.0 g), and it was used without further purifications.

b) (3R,8aR)-3-Bromomethyl-3-methyltetrahydropyrrolo[2,1-c][1,4]oxazine-1,4-dione

NBS (16 g, 89.9 mmol) was dissolved in DMF (50 ml) and added at room temperature to a solution of (2R)-1-(2-methylacryloyl)pyrrolidine-2-carboxylic acid

(11.5 g, contains 8.0 g of the corresponding starting material, 43.4 mmol) in DMF (50 ml). The mixture was stirred for 20 h and evaporated at 80-90 °C. The residue was mixed with water (250 ml) and extracted with ethyl acetate (4 x 80ml). The combined ethyl acetate phase was washed with 1 M $NaHCO_3$ solution (2 x 50 ml) and water (1 x 50 ml). The organic phase was dried over Na_2SO_4 and evaporated. The yield of the crude oil was 9.3 g. Ethyl acetate (10 ml) was added and the mixture was stirred in an ice bath. The precipitated product was filtered and washed with cooled ethyl acetate. The yield was 1.2 g. ^{1}H NMR (DMSO-d_6): 1.58 (3H, s), 1.75-2.10 (3H, m), 2.25 (1H, m), 3.30-3.55 (2H, m), 3.87 (1H, d, J=11.4 Hz), 4.03 (1H, d, J=11.4 Hz), 4.70 (1H, m).

c) (2R)-3-Bromo-2-hydroxy-2-methylpropionic acid

(3R,8aR)-3-Bromomethyl-3-methyltetrahydropyrrolo[2,1-c][1,4]oxazine-1,4-dione (1.1 g, 4.2 mmol) was dissolved in concentrated HCl (10 ml) and refluxed for 7 h. The mixture was cooled to room temperature. Water (20 ml) was added and the mixture was extracted with ethyl acetate (3 x 20 ml). The combined organic phase was evaporated and the residue was mixed with toluene (5 ml). The crystallised product was filtered and washed with toluene. The yield was 0.74 g. ^{1}H NMR (DMSO-d_6): 1.37 (3H, s), 3.54 (1H, d, J=10.2 Hz), 3.64 (1H, d, J=10.2 Hz), 5.35 (1H, bs), 12.80 (1H, bs).

d) (2R)-3-Bromo-2-hydroxy-2-methyl-N-(3-methyl-4-nitrophenyl)-propionamide

Thionyl chloride (0.48 ml, 6.6 mmol) was added dropwice to a solution of (2R)-3-Bromo-2-hydroxy-2-methylpropionic acid (1.0 g, 5.5 mmol) in 10 ml of DMA at –5 to –10 °C. The mixture was stirred for 2 h, and a solution of 3-methyl-4-nitroaniline (0.83 g, 5.5 mmol) in 7 ml of DMA was added to the above mixture. The resulting mixture was stirred for 3 h at room temperature and poured into water (250 ml). The aqueous phase was extracted with ethyl acetate (4 x 50 ml), dried over Na_2SO_4 and evaporated. The yield of the desired compound was 2.5 g (contains also DMA), and it was used without further purifications. ^{1}H NMR (DMSO-d_6): 1.48 (3H, s), 2.53 (3H, s), 3.58 (1H, d, J=10.4 Hz), 3.82 (1H, d, J=10.4 Hz), 6.34 (1H, bs), 7.86 (1H, dd, J=9.0 Hz and 2.2 Hz), 7.91 (1H, d, J=2.2 Hz), 8.04 (1H, d, J=9.0 Hz), 10.09 (1H, bs).

e) (2S)-3-(4-Acetylaminophenoxy)-2-hydroxy-2-methyl-N-(3-methyl-4-nitrophenyl)propionamide

A solution of 4-acetamidophenol 0.62 g, 4.1 mmol) in THF (7 ml) was added dropwise to a stirred suspension of sodium hydride (0.27 g, 6.8 mmol, 60 % dispersion in mineral oil) in THF (6 ml) and the temperature was kept below 5 °C during the addition. The mixture was stirred for 10 min and a solution of (2R)-3-bromo-2-hydroxy-2-methyl-N-(3-methyl-4-nitrophenyl)-propionamide (0.86 g, 2.7 mmol) in THF (7 ml) was added. The mixture was stirred at room temperature for 30 min and heated to 60 °C and stirred at this temperature for 5 h, and allowed to cool to the room temperature. The solvent was evaporated and the residue was dissolved to the mixture of water (80 ml) and ethyl acetate (80 ml). The pH was adjusted to 2 - 3 with 2 M HCl and the phases were separated. The organic phase was washed with 1 M Na_2CO_3 (6 x 30 ml), dried over Na_2SO_4 and evaporated. The oily residue was crystallised from ethyl acetate. The yield was 0.27 g. ^{1}H NMR (DMSO-d_6): 1.42 (3H, s), 1.99 (3H, s), 2.53 (3H, s), 3.93 (1H, d, J=9.6 Hz), 4.16 (1H, d, J=9.6 Hz), 6.20 (1H, bs), 6.84 (2H, d, J=9.0 Hz), 7.44 (2H, d, J=9.0 Hz), 7.88 (1H, dd, J=9.0 Hz and 2.3 Hz), 7.93 (1H, d, J=2.3 Hz), 8.04 (1H, d, J=9.0 Hz), 9.76 (1H, s), 10.15 (1H, bs).

Example 4.

(2S)-3-(4-Acetylamino-3-fluorophenoxy)-2-hydroxy-2-methyl-N-(3-methyl-4-nitrophenyl)propionamide

(2S)-3-(4-Acetylamino-3-fluorophenoxy)-2-hydroxy-2-methyl-N-(3-methyl-4-nitrophenyl)propionamide was prepared according to the method B as described in Example 3e starting from 4-acetylamino-3-fluorophenol and N-[3-methyl-4-(nitro)phenyl]-(2R)-3-bromo-2-hydroxy-2-methylpropanamide. ^{1}H NMR (DMSO-d_6): 1.42 (3H, s), 2.02 (3H, s), 2.53 (3H, s), 3.97 (1H, d, J=9.7 Hz), 4.21 (1H, d, J=9.7 Hz), 6.23 (1H, bs), 6.72 (1H, m), 6.90 (1H, m), 7.56 (1H, m), 7.88 (1H, dd, J=9.0 Hz and 2.2 Hz), 7.93 (1H, d, J=2.2 Hz), 8.03 (1H, d, J=9.0 Hz), 9.51 (1H, s), 10.15 (1H, bs).

Example 5.

4-[2-Hydroxy-2-(3-methyl-4-nitrophenylcarbamoyl)propoxy]benzamide

4-[2-Hydroxy-2-(3-methyl-4-nitrophenylcarbamoyl)propoxy]benzamide was prepared as described in Example 1 starting from 4-hydroxybenzamide and 1,2-epoxy-2-methyl-N-(3-methyl-4-nitrophenyl)-2-propanamide. ^{1}H-NMR (400 MHz, DMSO-d_6): 1.45 (3H, s), 2.53 (3H, s), 4.04 (1H, d, J = 9.7 Hz), 4.28 (1H, d, J = 9.7 Hz), 6.26 (1H, s), 6.94-6.98 (2H, m), 7.19 (1 H, br s), 7.80-7.83 (3H, m), 7.89 (1H, dd, J = 9.0 Hz, J = 2.2 Hz), 7.95 (1H, d, J = 2.0 Hz), 8.05 (1H, d, J = 9.0 Hz), 10.19 (1H, s).

Example 6.

3-(3,4-Dichlorophenoxy)-2-hydroxy-2-methyl-N-(3-methyl-4-nitrophenyl)-propionamide

3-(3,4-Dichlorophenoxy)-2-hydroxy-2-methyl-N-(3-methyl-4-nitrophenyl)-propionamide was prepared as described in Example 1 starting from 3,4-dichlorophenol and 1,2-epoxy-2-methyl-N-(3-methyl-4-nitrophenyl)-2-propanamide. ^{1}H-NMR (400 MHz, DMSO-d_6): 1.43 (3H, s), 2.53 (3H, s), 4.02 (1H, d, J = 9.9 Hz), 4.28 (1H, d, J = 9.9 Hz), 6.27 (1H, s), 6.95 (1H, dd, J = 8,9 Hz, J = 2,8 Hz), 7.25 (1 H, d, J = 2,8 Hz), 7.49 (1 H, d, J = 8,9 Hz), 7.88 (1H, dd, J = 9.0 Hz, J = 2.3 Hz), 7.93 (1H, d, J = 2.0 Hz), 8.04 (1H, d, J = 9.0 Hz), 10.17 (1H, s).

Example 7.

4-[2-Hydroxy-2-(3-methyl-4-nitrophenylcarbamoyl)propoxy]benzoic acid ethyl ester

4-[2-Hydroxy-2-(3-methyl-4-nitrophenylcarbamoyl)propoxy]benzoic acid ethyl ester was prepared as described in Example 1 starting from ethyl 4-hydroxybenzoate and 1,2-epoxy-2-methyl-N-(3-methyl-4-nitrophenyl)-2-propanamide. ^{1}H-NMR (400 MHz, DMSO-d_6): 1.30 (3H, t, J = 7.1 Hz), 1.45 (3H, s), 2.53 (3H, s), 4.07 (1H, d, J = 9.7 Hz), 4.26 (2H, q, J = 7.1 Hz), 4.30 (1H, d, J = 9.7 Hz), 6.29 (1H, s), 7.01-7.05 (2H, m), 7.86-7.91 (3H, m), 7.94 (1H, d, J = 1.9 Hz), 8.04 (1H, d, J = 9.0 Hz), 10.20 (1H, s).

Example 8.

3-(3-Chloro-4-fluorophenoxy)-2-hydroxy-2-methyl-N-(3-methyl-4-nitrophenyl)propionamide

3-(3-Chloro-4-fluorophenoxy)-2-hydroxy-2-methyl-N-(3-methyl-4-nitrophenyl)propionamide was prepared as described in Example 1 starting from 3-chloro-4-fluorophenol and 1,2-epoxy-2-methyl-N-(3-methyl-4-nitrophenyl)-2-propanamide. ^{1}H-NMR (400 MHz, DMSO-d_6): 1.42 (3H, s), 2.53 (3H, s), 4.00 (1H, d, J = 9.8 Hz), 4.25 (1H, d, J = 9.8 Hz), 6.21 (1H, s), 6.89-6.95(1H, m), 7.15-7.19 (1 H, m), 7.26-7.32 (1H, m), 7.87 (1H, dd, J = 8.9 Hz, J = 2.3 Hz), 7.91 (1H, d, J = 1.9 Hz), 8.03 (1H, d, J = 8.9 Hz), 10.12 (1H, s).

Example 9.

2-Hydroxy-2-methyl-N-(3-methyl-4-nitrophenyl)-3-(4-trifluoromethoxyphenoxy)propionamide

2-Hydroxy-2-methyl-N-(3-methyl-4-nitrophenyl)-3-(4-trifluoromethoxyphenoxy)propionamide was prepared as described in Example 1 starting from 4-(trifluoromethoxy)phenol and 1,2-epoxy-2-methyl-N-(3-methyl-4-nitrophenyl)-2-propanamide. ^{1}H-NMR (400 MHz, DMSO-d_6): 1.44 (3H, s), 2.53 (3H, s), 4.01 (1H, d, J = 9.7 Hz), 4.24 (1H, d, J = 9.7 Hz), 6.24 (1H, s), 6.99-7.05(2H, m), 7.22-7.30 (2 H, m), 7.88 (1H, dd, J = 8.9 Hz, J = 2.3 Hz), 7.93 (1H, d, J = 1.9 Hz), 8.03 (1H, d, J = 8.9 Hz), 10.14 (1H, s).

Example 10.

3-(2,3-Dichlorophenoxy)-2-hydroxy-2-methyl-N-(3-methyl-4-nitrophenyl)-propionamide

3-(2,3-Dichlorophenoxy)-2-hydroxy-2-methyl-N-(3-methyl-4-nitrophenyl)-propionamide was prepared as described in Example 1 starting from 2,3-dichlorophenol and 1,2-epoxy-2-methyl-N-(3-methyl-4-nitrophenyl)-2-propanamide. ^{1}H-NMR (400 MHz, DMSO-d_6): 1.46 (3H, s), 2.53 (3H, s), 4.16 (1H, d, J = 9.8 Hz), 4.27 (1H, d, J = 9.8 Hz), 6.27 (1H, s), 7.16-7.21(2H, m), 7.27-7.33 (1 H, m), 7.87 (1H, dd, J = 8.9 Hz, J = 2.3 Hz), 7.91 (1H, d, J = 1.9 Hz), 8.03 (1H, d, J = 8.9 Hz), 10.14 (1H, s)

Example 11.

3-(4-Fluorophenoxy)-2-hydroxy-2-methyl-N-(3-methyl-4-nitrophenyl)-propionamide

3-(4-Fluorophenoxy)-2-hydroxy-2-methyl-N-(3-methyl-4-nitrophenyl)-propionamide was prepared as described in Example 1 starting from *p*-fluorophenol and 1,2-epoxy-2-methyl-N-[3-methyl-4-nitrophenyl]-2-propanamide. ^{1}H-NMR (400 MHz, DMSO-d_6): 1.43 (3H, s), 2.53 (3H, s), 3.96 (1H, d, J = 9.6 Hz), 4.20 (1H, d, J = 9.6 Hz), 6.21 (1H, s), 6.90-6.96 (2H, m), 7.06-7.12 (2H, m), 7.89 (1H, dd, J = 9.0 Hz, J = 2.2 Hz), 7.90 (1H, d, J = 1.9 Hz), 8.04 (1H, d, J = 9.0 Hz), 10.15 (1H, s).

Example 12.

2-Hydroxy-2-methyl-N-(3-methyl-4-nitrophenyl)-3-*p*-tolyloxypropionamide

2-Hydroxy-2-methyl-N-(3-methyl-4-nitrophenyl)-3-*p*-tolyloxypropionamide was prepared as described in Example 1 starting from *p*-methylphenol and 1,2-epoxy-2-methyl-N-[3-methyl-4-nitrophenyl]-2-propanamide. ^{1}H-NMR (400 MHz, DMSO-d_6): 1.43 (3H, s), 2.21 (3H, s), 2.53 (3H, s), 3.93 (1H, d, J = 9.6 Hz), 4.17 (1H, d, J = 9.5 Hz), 6.18 (1H, s), 8.53 (2H, d, J = 8.5 Hz), 7.06 (2H, d, J = 8.4 Hz), 7.89 (1H, dd, J = 2.2 Hz, J = 9.0 Hz), 7.94 (1H, d, J = 1.8 Hz), 8.04 (1H, d, J = 9.0 Hz), 10.14 (1H, s).

Example 13.

2-Hydroxy-2-methyl-N-(3-methyl-4-nitrophenyl)-3-[4-(2,2,2-trifluoroacetyl-amino)phenoxy]propionamide

2-Hydroxy-2-methyl-N-(3-methyl-4-nitrophenyl)-3-[4-(2,2,2-trifluoroacetyl-amino)phenoxy]propionamide was prepared as described in Example 1 starting from *p*-N-trifluoroacetamidophenol and 1,2-epoxy-2-methyl-N-[3-methyl-4-nitrophenyl]-2-propanamide. ^{1}H-NMR (400 MHz, DMSO-d_6): 1.43 (3H, s), 2.53 (3H, s), 3.98 (1H, d, J = 9.6 Hz), 4.22 (1H, d, J = 9.6 Hz), 6.22 (1H, s), 6.93-6.98 (2H, m), 7.52-7.56 (2H, m), 7.88 (1H, dd, J = 9.0 Hz, J = 2.2 Hz), 7.93 (1H, d, J = 1.9 Hz), 8.04 (1H, d, J = 9.0 Hz).

Example 14.

2-Hydroxy-2-methyl-N-(3-methyl-4-nitrophenyl)-3-phenoxypropionamide

2-Hydroxy-2-methyl-N-(3-methyl-4-nitrophenyl)-3-phenoxypropionamide was prepared as described in Example 1 starting from phenol and 1,2-epoxy-2-

methyl-N-[3-methyl-4-nitrophenyl]-2-propanamide. ^{1}H-NMR (400 MHz, DMSO-d_6): 1.44 (3H, s), 2.53 (3H, s), 3.97 (1H, d, J = 9.6 Hz), 4.21 (1H, d, J = 9.6 Hz), 6.21 (1H, s), 6.90-6.95 (3H, m), 7.24-7.29 (2H, m), 7.89 (1H, dd, J = 2.3 Hz, J = 9.0 Hz), 7.94 (1H, d, J = 2.0 Hz), 8.04 (1H, d, ^3J = 9.0 Hz), 10.16 (1H, s).

Example 15.

2-Hydroxy-2-methyl-N-(3-methyl-4-nitrophenyl)-3-(4-trifluoromethyl-phenoxy)propionamide

2-Hydroxy-2-methyl-N-(3-methyl-4-nitrophenyl)-3-(4-trifluoromethyl-phenoxy)propionamide was prepared as described in Example 1 starting from *p*-hydroxybenzotrifluoride and 2-methyloxirane-2-carbocylic acid (3-methyl-4-nitrophenyl)amide. The crude product was purified by flash chromatography using heptane/ethyl acetate (95:5) as eluent. Crystallization from toluene. ^{1}H NMR (400 MHz, $CDCl_3$): 1.62 (3H, s), 2.65 (3H, s), 3.25 (1H, s, -OH), 4.05 (1H, d, $^2J_{gem}$ = 9.1 Hz), 4.51 (1H, d, $^2J_{gem}$ = 9.0 Hz), 7.00 (2H, d, ^3J = 8.8 Hz), 7.57 (2H, d, ^3J = 8.8 Hz), 7.58 (1H, dd, ^3J = 8.9 Hz, ^4J = 2.7 Hz), 7.66 (1H, d, ^4J = 2.2 Hz), 8.08 (1H, d, ^3J = 8.9 Hz), 8.9 (1H, broad s, -NHCO-).

Example 16.

3-(4-Acetylphenoxy)-2-hydroxy-2-methyl-N-(3-methyl-4-nitrophenyl)-propionamide

3-(4-Acetylphenoxy)-2-hydroxy-2-methyl-N-(3-methyl-4-nitrophenyl)-propionamide was prepared as described in Example 1 starting from 4′-hydroxy-acetophenone and 2-methyloxirane-2-carbocylic acid (3-methyl-4-nitrophenyl)amide. The crude product was purified by flash chromatography using heptane/ethyl acetate (95:5) as eluent. Crystallization from toluene, m.p. 153-155 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 1.62 (3H, s), 2.57 (3H, s), 2.65 (3H, s), 3.26 (1H, s, -OH), 4.07 (1H, d, $^2J_{gem}$ = 9.1 Hz), 4.53 (1H, d, $^2J_{gem}$ = 9.1 Hz), 6.96 (2H, d, ^3J = 8.9 Hz), 7.58 (1H, dd, ^3J = 8.9 Hz, ^4J = 2.4 Hz), 7.66 (1H, d, ^4J = 2.3 Hz), 7.94 (2H, d, ^3J = 8.9 Hz), 8.09 (1H, d, ^3J = 9.0 Hz), 8.95 (1H, broad s, -NHCO-).

Example 17.

3-(4-Cyanophenoxy)-2-hydroxy-2-methyl-N-(3-methyl-4-nitrophenyl)-propionamide

3-(4-Cyanophenoxy)-2-hydroxy-2-methyl-N-(3-methyl-4-nitrophenyl)-propionamide was prepared as described in Example 1 starting from 4-cyanophenol and 2-methyloxirane-2-carbocylic acid (3-methyl-4-nitrophenyl)amide. The crude product was purified by flash chromatography using heptane/ethyl acetate as a gradient eluent. Crystallization from toluene. ^{1}H NMR (400 MHz, DMSO-d_6): 1.44 (3H, s), 2.53 (3H, s), 4.08 (1H, d, $^2J_{gem}$ = 9.8 Hz), 4.33 (1H, d, $^2J_{gem}$ = 9.9 Hz), about 6.3 (1H, broad s, -OH), 7.10 (2H, d, ^3J = 8.8 Hz), 7.75 (2H, d, ^3J = 8.8 Hz), 7.88 (1H, dd, ^3J = 9.0 Hz, ^4J = 2.3 Hz), 7.93 (1H, d, ^4J = 2.0 Hz), 8.04 (1H, d, ^3J = 9.0 Hz), about 10.2 (1H, broad s, -NHCO-).

Example 18.

3-(3-Fluorophenoxy)-2-hydroxy-2-methyl-N-(3-methyl-4-nitrophenyl)-propionamide

3-(3-Fluorophenoxy)-2-hydroxy-2-methyl-N-(3-methyl-4-nitrophenyl)-propionamide was prepared as described in Example 1 starting from 3-fluorophenol and 2-methyloxirane-2-carbocylic acid (3-methyl-4-nitrophenyl)amide. The crude product was purified by flash chromatography using heptane/ethyl acetate as a gradient eluent. Crystallization from toluene/heptane, m.p. 83-86 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 1.43 (3H, s), 2.53 (3H, s), 3.99 (1H, d, $^2J_{gem}$ = 9.7 Hz), 4.24 (1H, d, $^2J_{gem}$ = 9.7 Hz), 6.26 (1H, broad s, -OH), 6.73-7.78 (2H, m), 6.81 (1H, m), 7.28 (1H, m), 7.89 (1H, dd, ^3J = 9.0 Hz, ^4J = 2.3 Hz), 7.94 (1H, d, ^4J = 2.0 Hz), 8.04 (1H, d, ^3J = 8.9 Hz), 10.17 (1H, broad s, -NHCO-).

Example 19.

3-(2-Fluorophenoxy)-2-hydroxy-2-methyl-N-(3-methyl-4-nitrophenyl)-propionamide

3-(2-Fluorophenoxy)-2-hydroxy-2-methyl-N-(3-methyl-4-nitrophenyl)-propionamide was prepared as described in Example 1 starting from 2-fluorophenol and 2-methyloxirane-2-carbocylic acid (3-methyl-4-nitrophenyl)amide. The crude product was purified by flash chromatography using heptane/ethyl acetate (90:10) as eluent. Crystallization from ethyl acetate/heptane, m.p. 94-96 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 1.44 (3H, s), 2.53 (3H, s), 4.07 (1H, d, $^2J_{gem}$ = 9.8 Hz), 4.27 (1H, d, $^2J_{gem}$ = 9.8 Hz), 6.27 (1H, broad s, -OH), 6.93 (1H, m), 7.10 (1H, m), 7.14-7.21

(2H, m), 7.88 (1H, dd, ^3J = 9.0 Hz, ^4J = 2.2 Hz), 7.93 (1H, d, ^4J = 2.0 Hz), 8.04 (1H, d, ^3J = 9.0 Hz), 10.17 (1H, broad s, -NHCO-)

Example 20.

2-Hydroxy-3-[4-(2-hydroxyethyl)phenoxy]-2-methyl-N-(3-methyl-4-nitrophenyl)propionamide

2-Hydroxy-3-[4-(2-hydroxyethyl)phenoxy]-2-methyl-N-(3-methyl-4-nitrophenyl)propionamide was prepared as described in Example 1 starting from 4-hydroxyphenyl alcohol (1.45 eq.), sodium hydride (2.9 eq.) and 2-methyloxirane-2-carbocylic acid (3-methyl-4-nitrophenyl)amide (1 eq.). The crude product was purified by flash chromatography using heptane/ethyl acetate as a gradient eluent (90:10 – 40:60). ^{1}H NMR (400 MHz, DMSO-d_6): 1.43 (3H, s), 2.53 (3H, s), 2.63 (2H, t, ^3J = 7.1 Hz), 3.53 (2H, m), 3.94 (1H, d, $^2J_{gem}$ = 9.6 Hz), 4.17 (1H, d, $^2J_{gem}$ = 9.6 Hz), 4.56 (1H, t, ^3J = 5.2 Hz, $CH_2O\underline{H}$), 6.17 (1H, broad s, -OH), 6.81 (2H, d, ^3J = 8.7 Hz), 7.09 (2H, d), 7.88 (1H, dd, ^3J = 9.0 Hz, ^4J = 2.3 Hz), 7.93 (1H, d, ^4J = 1.9 Hz), 8.04 (1H, d, ^3J = 9.0 Hz), 10.13 (1H, broad s, -NHCO-).

Example 21.

3-(2,6-Dichlorophenoxy)-2-hydroxy-2-methyl-N-(3-methyl-4-nitrophenyl)-propionamide

3-(2,6-Dichlorophenoxy)-2-hydroxy-2-methyl-N-(3-methyl-4-nitrophenyl)-propionamide was prepared as described Example 1 starting from 2,6-dichlorophenol and 1,2-epoxy-2-methyl-N-(3-methyl-4-nitrophenyl)-2-propanamide.^{1}H-NMR (400 MHz, DMSO-d_6): 1.47 (3H, s), 2.53 (3H, s), 4.12 (1H, d, J = 9.0 Hz), 4.18 (1H, d, J = 9.0 Hz), 6.14 (1H, s), 7.12-7.18 (1H, m), 7.43-7.46 (2 H, m), 7.86-7.90 (2H, m), 8.02-8.05 (1H, m), 10.11 (1H, s).

Example 22.

3-(4-Bromo-2-fluorophenoxy)-2-hydroxy-2-methyl-N-(3-methyl-4-nitrophenyl)propionamide

3-(4-Bromo-2-fluorophenoxy)-2-hydroxy-2-methyl-N-(3-methyl-4-nitrophenyl)propionamide was prepared as described in Example 1 starting from 4-bromo-2-fluorophenol and 1,2-epoxy-2-methyl-N-(3-methyl-4-nitrophenyl)-2-

propanamide. ^{1}H-NMR (400 MHz, DMSO-d_6): 1.43 (3H, s), 2.53 (3H, s), 4.08 (1H, d, J = 9.9 Hz), 4.28 (1H, d, J = 9.9 Hz), 6.26 (1H, s), 7.15-7.22 (1H, m), 7.29-7.33 (1 H, m), 7.46-7.50 (1H, m), 7.86 (1H, dd, J = 8.9 Hz, J = 2.3 Hz), 7.88 (1H, d, J = 1.9 Hz), 8.03 (1H, J = 8.9 Hz), 10.13 (1H, s).

Example 23.

3-(4-Chlorophenoxy)-2-hydroxy-2-methyl-N-(3-methyl-4-nitrophenyl)-propionamide

3-(4-Chlorophenoxy)-2-hydroxy-2-methyl-N-(3-methyl-4-nitrophenyl)-propionamide was prepared as described in Example 1 starting from *p*-chlorophenol and 1,2-epoxy-2-methyl-N-[3-methyl-4-nitrophenyl]-2-propanamide. ^{1}H-NMR (400 MHz, DMSO-d_6): 1.43 (3H, s), 2.53 (3H, s), 3.98 (1H, d, *J* = 9.7 Hz), 4.22 (1H, d, *J* = 9.7 Hz), 6.23 (1H, s), 6.93-7.00 (2H, m), 7.28-7.32 (2H, m), 7.88 (1H, dd, *J* = 9.0 Hz, *J* = 2.2 Hz), 7.93 (1H, d, *J* = 1.9 Hz), 8.04 (1H, d, *J* = 9.0 Hz), 10.51 (1H, s).

Example 24.

3-(4-Bromophenoxy)-2-hydroxy-2-methyl-N-(3-methyl-4-nitrophenyl)-propionamide

3-(4-Bromophenoxy)-2-hydroxy-2-methyl-N-(3-methyl-4-nitrophenyl)-propionamide was prepared as described in Example 1 starting from *p*-bromrophenol and 1,2-epoxy-2-methyl-N-[3-methyl-4-nitrophenyl]-2-propanamide. ^{1}H-NMR (400 MHz, DMSO-d_6): 1.43 (3H, s), 2.53 (3H, s), 3.97 (1H, d, *J* = 9.7 Hz), 4.21 (1H, d, *J* = 9.7 Hz), 6.23 (1H, s), 6.88-6.93 (2H, m), 7.39-7.44 (2H, m), 7.88 (1H, dd, *J* = 9.0 Hz, *J* = 2.2 Hz), 7.93 (1H, d, *J* = 1.8 Hz), 8.04 (1H, d, *J* = 9.0 Hz), 10.15 (1H, s).

Example 25.

2-Hydroxy-3-(4-methoxyphenoxy)-2-methyl-N-(3-methyl-4-nitrophenyl)-propionamide

2-Hydroxy-3-(4-methoxyphenoxy)-2-methyl-N-(3-methyl-4-nitrophenyl)-propionamide was prepared as described in Example 1 starting from *p*-methoxy-phenol and 1,2-epoxy-2-methyl-N-[3-methyl-4-nitrophenyl]-2-propanamide. ^{1}H-NMR (400 MHz, DMSO-d_6): 1.42 (3H, s), 2.53 (3H, s), 3.68 (3H, s), 3.91 (1H, d, *J* =

9.5 Hz), 4.15 (1H, d, J = 9.5 Hz), 6.17 (1H, s), 6.80-6.87 (4H, m), 7.88 (1H, dd, J = 9.0 Hz, J = 2.2 Hz), 7.93 (1H, d, J = 2.0 Hz), 8.04 (1H, d, J = 9.0 Hz), 10.13 (1H, s).

Example 26.

3-(Benzo[1,3]dioxol-5-yloxy)-2-hydroxy-2-methyl-N-(3-methyl-4-nitrophenyl)propionamide

3-(Benzo[1,3]dioxol-5-yloxy)-2-hydroxy-2-methyl-N-(3-methyl-4-nitrophenyl)-propionamide was prepared as described in Example 1 starting from 3,4-methylenedioxylphenol and 1,2-epoxy-2-methyl-N-[3-methyl-4-nitrophenyl]-2-propanamide. ^{1}H-NMR (400 MHz, DMSO-d_6): 1.41 (3H, s), 2.53 (3H, s), 3.90 (1H, d, J = 9.6 Hz), 4.15 (1H, d, J = 9.6 Hz), 5.94 (2H, s), 6.18 (1H, s), 6.35 (1H, dd, J = 8.5 Hz, J = 2.5 Hz), 6.59 (1H, d, J = 2.5 Hz), 6.78 (1H, d, J = 8.5 Hz), 7.88 (1H, dd, J = 9.0 Hz, J = 2.2 Hz), 7.93 (1H, d, J = 1.6 Hz), 8.04 (1H, d, J = 9.0 Hz), 10.13 (1H, s).

Example 27.

3-(3,4-Dimethoxyphenoxy)-2-hydroxy-2-methyl-N-(3-methyl-4-nitrophenyl)-propionamide

3-(3,4-Dimethoxyphenoxy)-2-hydroxy-2-methyl-N-(3-methyl-4-nitrophenyl)-propionamide was prepared as described in Example 1 starting from 3,4-dimethoxy-phenol and 1,2-epoxy-2-methyl-N-[3-methyl-4-nitrophenyl]-2-propanamide. ^{1}H-NMR (400 MHz, DMSO-d_6): 1.43 (3H, s), 2.53 (3H, s), 3.67 (3H, s), 3.70 (3H, s), 3.91 (1H, d, J = 9.6 Hz), 4.17 (1H, d, J = 9.6 Hz), 6.17 (1H, s), 6.42 (1H, dd, J = 8.8 Hz, J = 2.8 Hz), 6.52 (1H, d, J = 2.8 Hz), 6.82 (1H, d, J = 8.8 Hz), 7.89 (1H, dd, J = 9.0 Hz, J = 2.2 Hz), 7.94 (1H, d, J = 1.9 Hz), 8.04 (1H, d, J = 9.0 Hz), 10.13 (1H, s).

Example 28.

3-(3,4-Difluorophenoxy)-2-hydroxy-2-methyl-N-(3-methyl-4-nitrophenyl)-propionamide

3-(3,4-Difluorophenoxy)-2-hydroxy-2-methyl-N-(3-methyl-4-nitrophenyl)-propionamide was prepared as described in Example 1 starting from 3,4-difluoro-phenol and 1,2-epoxy-2-methyl-N-[3-methyl-4-nitrophenyl]-2-propanamide. ^{1}H-NMR (400 MHz, DMSO-d_6): 1.43 (3H, s), 2.53 (3H, s), 3.97 (1H, d, J = 9.8 Hz),

4.23 (1H, d, J = 9.8 Hz), 6.24 (1H, s), 6.72-6.79 (1H, m), 7.02-7.10 (1H, m), 7.20-7.33 (1H, m), 7.88 (1H, dd, J = 9.0 Hz, J = 2.2 Hz), 7.93 (1H, d, J = 1.9 Hz), 8.04 (1H, d, J = 9.9 Hz), 10.15 (1H, s).

Example 29.

3-(2,4-Dichloro-3,5-dimethylphenoxy)-2-hydroxy-2-methyl-N-(3-methyl-4-nitrophenyl)-propionamide

3-(2,4-Dichloro-3,5-dimethylphenoxy)-2-hydroxy-2-methyl-N-(3-methyl-4-nitrophenyl)-propionamide was prepared as described in Example 1 starting from 2,4-dichloro-3,5-dimethylphenol and 1,2-epoxy-2-methyl-N-[3-methyl-4-nitro-phenyl]-2-propanamide. ^{1}H-NMR (400 MHz, DMSO-d_6): 1.46 (3H, s), 2.31 (3H, s), 2.36 (3H, s), 2.53 (3H, s), 4.41 (1H, d, J = 9.7 Hz), 4.21 (1H, d, J = 9.7 Hz), 6.25 (1H, s), 7.87 (1H, dd, J = 9.0 Hz, J = 2.3 Hz), 7.91 (1H, d, J = 1.9 Hz), 8.04 (1H, d, J = 9.0 Hz), 10.12 (1H, s).

Example 30.

3-(6-Bromonaphtalen-2-yloxy)-2-hydroxy-2-methyl-N-(3-methyl-4-nitrophenyl)-propionamide

3-(6-Bromonaphtalen-2-yloxy)-2-hydroxy-2-methyl-N-(3-methyl-4-nitro-phenyl)-propionamide was prepared as described in Example 1 starting from 6-bromo-2-naphtol and 1,2-epoxy-2-methyl-N-[3-methyl-4-nitrophenyl]-2-propan-amide. ^{1}H-NMR (400 MHz, DMSO-d_6): 1.49 (3H, s), 2.53 (3H, s), 4.11 (1H, d, J = 9.7 Hz), 4.35 (1H, d, J = 9.7 Hz), 6.29 (1H, s), 7.18 (1H, dd, J = 9.0 Hz, J = 2.5 Hz), 7.41 (1H, d, J = 2.4 Hz), 7.57 (1H, dd, J = 8.7 Hz, J = 2.0 Hz), 7.77 (1H, d, J = 9.1 Hz), 7.80 (1H, d, J = 9.3 Hz), 7.90 (1H, dd, J = 9.0 Hz, J = 2.2 Hz), 7.95 (1H, d, 1.9 Hz), 8.05 (1H, d, J = 9.0 Hz), 8.10 (1H, d, J = 1.9 Hz), 10.21 (1H, s).

Example 31.

3-(4-Acetylamino-3-trifluoromethylphenoxy)-2-hydroxy-2-methyl-N-(3-methyl-4-nitrophenyl)propionamide

a) 4-Amino-3-trifluoromethylphenol

4-Nitro-3-trifluoromethylphenol (0.414 g; 2.0 mmol) was dissolved in 25 ml of glacial acetic acid and Zinc dust (2,62 g; 40 mmol) was added in small portions during 10 minutes allowing the temperature to rise up to +40°C. The mixture was stirred for ten minutes and filtered. The dust was washed with 3 × 10 ml of glacial acetic acid and filtrate was evaporated to dryness to give 0.212 g of 4-amino-3-trifluoromethylphenol. ^{1}H-NMR (400 MHz, DMSO-d_6): 4.86 (2H, s), 6.72 (1H, d, J = 8.7 Hz), 6.74 (1H, d, J = 2.6 Hz), 6.78 (1H, dd, J = 8.7 Hz, J = 2.7 Hz), 8.91 (1H, s)

b) N-(4-Hydroxy-2-trifluoromethylphenyl)acetamide

4-Amino-3-trifluoromethylphenol (0.212 g; 1.2 mmol) was dissolved in 10 ml of glacial acetic acid under nitrogen athmosphere and acetic anhydride (0.3 ml; 3.0 mmol) was added followed with stirring for an hour at room temperature. Water (0.5 ml) was added into the reaction mixture and then evaporated to dryness. Toluene (50 ml) was added and the evaporation was repeated to give a quantitative yield of pure N-(4-Hydroxy-2-trifluoromethylphenyl)acetamide. ^{1}H-NMR (400 MHz, DMSO-d_6): 1.99 (3H, s), 7.01 (1H, dd, J = 8.6 Hz, J = 2.6 Hz), 7.02 (1H, d, J = 2.5 Hz), 7.19 (1H, d, J = 8.4 Hz), 9.33 (1H, s), 10.08 (1H, br s).

c) 3-(4-Acetylamino-3-trifluoromethylphenoxy)-2-hydroxy-2-methyl-N-(3-methyl-4-nitrophenyl)propionamide

3-(4-Acetylamino-3-trifluoromethylphenoxy)-2-hydroxy-2-methyl-N-(3-methyl-4-nitrophenyl)propionamide was prepared as described in Example 1 starting from N-(4-Hydroxy-2-trifluoromethylphenyl)-acetamide and 1,2-epoxy-2-methyl-N-[3-methyl-4-nitrophenyl]-2-propanamide. ^{1}H-NMR (400 MHz, DMSO-d_6): 1.46 (3H, s), 2.00 (3H, s), 2.53 (3H, s), 4.07 (1H, d, J = 9.8 Hz), 4.32 (1H, d, J = 9.8 Hz), 6.27 (1H, s), 7.19 (1H, d, J = 2.7 Hz), 7.22 (1H, dd, J = 9.0 Hz, J = 2.5 Hz), 7.31 (1H, d, J = 8.7 Hz), 7.88 (1H, dd, J = 9.0 Hz, J = 2.3 Hz), 7.93 (1H, d, J = 2.0 Hz), 8.04 (1H, d, J = 9.0 Hz), 9.43 (1H, s), 10.17 (1H, s).

Example 32.

2-Hydroxy-2-methyl-N-(3-methyl-4-nitrophenyl)-3-(3,4,5-trifluorophenoxy)-propionamide

2-Hydroxy-2-methyl-N-(3-methyl-4-nitrophenyl)-3-(3,4,5-trifluorophenoxy)-propionamide was prepared as described in Example 1 starting from 3,4,5-trifluorophenol and 1,2-epoxy-2-methyl-N-[3-methyl-4-nitrophenyl]-2-propanamide. ^{1}H-NMR (400 MHz, DMSO-d_6): 1.42 (3H, s), 2.53 (3H, s), 3.98 (1H, d, J = 9.9 Hz), 4.26 (1H, d, J = 9.0 Hz), 6.27 (1H, s), 6.92-7.02 (2H, m), 7.88 (1H, dd, J = 9.0 Hz, J = 2.2 Hz), 7.92 (1H, d, J = 1.9 Hz), 8.04 (1H, d, J = 9.0 Hz), 10.14 (1H, s).

Example 33.

2-Hydroxy-3-(1H-indol-5-yloxy)-2-methyl-N-(3-methyl-4-nitrophenyl)-propionamide

2-Hydroxy-3-(1H-indol-5-yloxy)-2-methyl-N-(3-methyl-4-nitrophenyl)-propionamide was prepared as described in Example 1 starting from 4-hydroxyindole and 1,2-epoxy-2-methyl-N-[3-methyl-4-nitrophenyl]-2-propanamide. ^{1}H-NMR (400 MHz, DMSO-d_6): 1.49 (3H, s), 2.53 (3H, s), 4.10 (1H, d, J = 9.4 Hz), 4.23 (1H, d, J = 9.4 Hz), 6.22 (1H, s), 6.31 (1H, d, J = 2.2 Hz), 6.47 (1H, dd, J = 6.8 Hz, J = 1.5 Hz), 6.93-7.00 (2H, m), 7.12-7.17 (1H, m), 7.92 (1H, dd, J = 9.0 Hz, J = 2.1 Hz), 7.98 (1H, d, J = 1.6 Hz), 8.05 (1H, d, J = 9.0 Hz), 10.24 (1H, s), 11.02 (1H, s).

Example 34.

2-Hydroxy-2-methyl-N-(3-methyl-4-nitrophenyl)-3-(4-methylsulfanyl-phenoxy)propionamide

2-Hydroxy-2-methyl-N-(3-methyl-4-nitrophenyl)-3-(4-methylsulfanyl-phenoxy)propionamide was prepared as described in Example 1 starting from 4-(methylthio)-phenol and 1,2-epoxy-2-methyl-N-[3-methyl-4-nitrophenyl]-2-propanamide. ^{1}H-NMR (400 MHz, DMSO-d_6): 1.43 (3H, s), 2.41 (3H, s), 2.53 (3H, s), 3.96 (1H, d, J = 9.6 Hz), 4.20 (1H, d, J = 9.6 Hz), 6.21 (1H, s), 6.87-6.93 (2H, m), 7.17-7.25 (2H, m), 7.88 (1H, dd, J = 9.0 Hz, J = 2.3 Hz), 7.93 (1H, d, J = 2.0 Hz), 8.04 (1H, d, J = 9.0 Hz), 10.15 (1H, s).

Example 35.

3-(3-Fluoro-4-nitro-phenoxy)-2-hydroxy-2-methyl-N-(3-methyl-4-nitro-phenyl)propionamide

3-(3-Fluoro-4-nitro-phenoxy)-2-hydroxy-2-methyl-N-(3-methyl-4-nitro-phenyl)-propionamide was prepared as described in Example 1 starting from 3-fluoro-4-nitrophenol and 2-methyl-oxirane-2-carboxylic acid (3-methyl-4-nitro-phenyl)amide. ^{1}H NMR (DMSO-d_6): 1.46 (3H, s), 2.53 (3H, s), 4.16 (1H, d, J=10.1 Hz), 4.41 (1H, d, J=10.1 Hz), 6.36 (1H, bs), 6.96 (1H, m), 7.22 (1H, m), 7.88 (1H, dd, J=9.0 Hz and 2.1 Hz), 7.90 (1H, d, J=2.1 Hz), 8.04 (1H, d, J=9.0 Hz), 8.24 (1H, m), 10.19 (1H, s).

Example 36.

3-[4-(4-Chlorobenzoyl)phenoxy]-2-hydroxy-2-methyl-N-(3-methyl-4-nitrophenyl)propionamide

3-[4-(4-Chlorobenzoyl)phenoxy]-2-hydroxy-2-methyl-N-(3-methyl-4-nitrophenyl)propionamide was prepared as described in Example 1 starting from 4-chloro-4´-hydroxybenzophenone and 2-methyloxirane-2-carbocylic acid (3-methyl-4-nitrophenyl)amide. The crude product was purified by flash chromatography using heptane/ethyl acetate as a gradient eluent. Crystallization from isopropanol. ^{1}H NMR (400 MHz, DMSO-d_6): 1.46 (3H, s), 2.53 (3H, s), 4.11 (1H, d, $^2J_{gem}$ = 9.7 Hz), 4.33 (1H, d, $^2J_{gem}$ = 9.7 Hz), about 6.3 (1H, broad s, -OH), 7.09 (2H, d, ^3J = 8.8 Hz), 7.62 (2H, d, ^3J = 8.5 Hz), 7.70 (2H, d, ^3J = 8.6 Hz), 7.72 (2H, d, ^3J = 9.0 Hz), 7.89 (1H, dd, ^3J = 9.0 Hz, ^4J = 2.3 Hz), 7.94 (1H, d, ^4J = 2.2 Hz), 8.05 (1H, d, ^3J = 9.0 Hz), about 10.2 (1H, broad s, -NHCO-).

Example 37.

3-(3-Chlorophenoxy)-2-hydroxy-2-methyl-N-(3-methyl-4-nitrophenyl)-propionamide

3-(3-Chlorophenoxy)-2-hydroxy-2-methyl-N-(3-methyl-4-nitrophenyl)-propionamide was prepared as described in Example 1 starting from 3-chlorophenol and 2-methyloxirane-2-carbocylic acid (3-methyl-4-nitrophenyl)amide. The crude product was purified by flash chromatography using heptane/ethyl acetate as a gradient eluent (10:90 - 40:90). Crystallization from toluene, m.p. 104-107 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 1.43 (3H, s), 2.53 (3H, s), 4.00 (1H, d, $^2J_{gem}$ = 9.8 Hz), 4.26 (1H, d, $^2J_{gem}$ = 9.8 Hz), 6.25 (1H, broad s, -OH), 6.88-6.91 (1H, m), 6.97-7.00 (1H, m), 7.02 (1H, t, ^4J = 2.1 Hz), 7.28 (1H, t, ^3J = 8.2 Hz), 7.89 (1H, dd, ^3J = 9.0

Hz, ^4J = 2.3 Hz), 7.94 (1H, d, ^4J = 2.2 Hz), 8.04 (1H, d, ^3J = 9.0 Hz), 10.17 (1H, broad s, -NHCO-).

Example 38.

2-Hydroxy-2-methyl-N-(3-methyl-4-nitrophenyl)-3-pentafluorophenyloxy-propionamide

2-Hydroxy-2-methyl-N-(3-methyl-4-nitrophenyl)-3-pentafluorophenyloxy-propionamide was prepared as described in Example 1 starting from pentafluorophenol and 1,2-epoxy-2-methyl-N-[3-methyl-4-nitrophenyl]-2-propanamide. ^{1}H-NMR (400 MHz, DMSO-d_6): 1.40 (3H, s), 2.53 (3H, s), 4.24 (1H, d, J = 10,2 Hz), 4.44 (1H, d, J = 10,2 Hz), 6.28 (1H, s), 7.87 (1H, dd, J = 9.0 Hz, J = 2.1 Hz), 7.89 (1H, d, J = 2.1 Hz), 8.05 (1H, d, J = 8.9 Hz), 10.13 (1H, s).

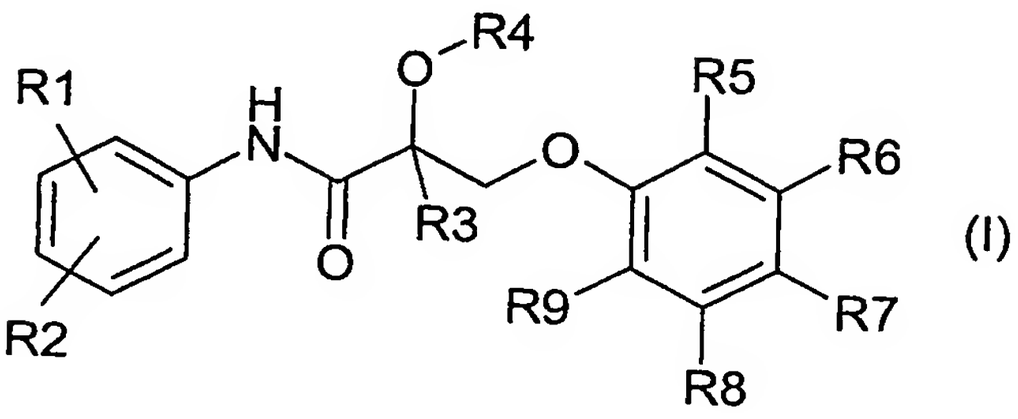
Example 39.

(2*S*)-3-(4-Fluorophenoxy)-2-hydroxy-2-methyl-N-(3-methyl-4-nitrophenyl)-propionamide

(2*S*)-3-(4-Fluorophenoxy)-2-hydroxy-2-methyl-N-(3-methyl-4-nitrophenyl)-propionamide was prepared as described in Example 3 starting from *p*-fluorophenol and (2R)-3-Bromo-2-hydroxy-2-methylpropanoic acid. ^{1}H-NMR (400 MHz, DMSO-d_6): 1.43 (3H, s), 2.53 (3H, s), 3.95 (1H, d, J = 9.6 Hz), 4.20 (1H, d, J = 9.6 Hz), 6.21 (1H, s), 6.90-6.97 (2H, m), 7.06-7.12 (2H, m), 7.88 (1H, dd, J = 9.0 Hz, J = 2.3 Hz), 7.93 (1H, d, J = 1.9 Hz), 8.04 (1H, d, J = 9.0 Hz), 10.15 (1H, s).

Claims

1. Compounds of formula (I)



(I)

wherein

R_1 is $(C_1\text{-}C_7)$alkyl;

R_2 is nitro, cyano or halogen;

R_3 is hydrogen, $(C_1\text{-}C_7)$alkyl or halo$(C_1\text{-}C_7)$alkyl;

R_4 is hydrogen, $(C_1\text{-}C_7)$alkyl, COR_{10} or SO_2R_{13};

R_5, R_6, R_7, R_8 and R_9 are independently hydrogen, halogen, nitro, cyano, $(C_1\text{-}C_7)$alkyl, halo$(C_1\text{-}C_7)$alkyl, cyano$(C_1\text{-}C_7)$alkyl, amino, mono- or di$(C_1\text{-}C_7)$alkyl-amino, amino$(C_1\text{-}C_7)$alkyl, hydroxy$(C_1\text{-}C_7)$alkyl, $-NHCOR_{10}$, $-N(COR_{10})_2$, $-COR_{11}$, $-OR_{12}$, OSO_2R_{13}, SO_2R_{14} or SR_{15} or an imide ring; or R_5 and R_6, R_6 and R_7, R_7 and R_8, or R_8 and R_9 form, together with any of the ring atom(s) to which they are attached, a condensed 5 to 7 membered aliphatic or aromatic carbocyclic ring or a condensed 5 to 7 membered heterocyclic ring containing 1 to 3 heteroatom(s) selected from N, O and S;

R_{10} and R_{11} are independently $(C_1\text{-}C_7)$alkyl, $(C_2\text{-}C_7)$alkenyl, halo$(C_1\text{-}C_7)$alkyl, $(C_6\text{-}C_{10})$aryl, $-N(R_{16})_2$ or $-OR_{17}$;

R_{12} and R_{15} are independently hydrogen, $(C_1\text{-}C_7)$alkyl, $(C_2\text{-}C_7)$alkenyl, halo$(C_1\text{-}C_7)$alkyl, amino$(C_1\text{-}C_7)$alkyl, mono- or di$(C_1\text{-}C_7)$alkylamino$(C_1\text{-}C_7)$alkyl, $(C_6\text{-}C_{10})$aryl, $-COR_{18}$;

R_{13} and R_{14} are independently $(C_1\text{-}C_7)$alkyl or $(C_2\text{-}C_7)$alkenyl, halo$(C_1\text{-}C_7)$alkyl or $(C_6\text{-}C_{10})$aryl;

R_{16} and R_{17} are independently hydrogen, $(C_1\text{-}C_7)$alkyl, $(C_2\text{-}C_7)$alkenyl, halo$(C_1\text{-}C_7)$alkyl , amino$(C_1\text{-}C_7)$alkyl or $(C_6\text{-}C_{10})$aryl;

R_{18} is $(C_1\text{-}C_7)$alkyl, $(C_2\text{-}C_7)$alkenyl, halo$(C_1\text{-}C_7)$alkyl or $(C_6\text{-}C_{10})$aryl;

and wherein each aryl or ring residue defined above may be substituted;

and pharmaceutically acceptable salts and esters thereof.

2. A compound according to claim1, wherein R_1 is methyl and R_2 is nitro.

3. A compound according to claim1 or 2, wherein R_4 is hydrogen and R_3 is methyl.

4. A compound according to any of claims 1 to 3, wherein R_5, R_6, R_7, R_8 and R_9 are independently hydrogen, halogen, cyano, (C_1-C_7)alkyl, (C_1-C_7)alkoxy, halo(C_1-C_7)alkyl, hydroxy(C_1-C_7)alkyl or -NHCOR$_{10}$, wherein R_{10} is (C_1-C_7)alkyl or halo(C_1-C_7)alkyl.

5. A compound according to claim 4, wherein at least one of R_5, R_6, R_7, R_8 and R_9 is a halogen.

6. A compound according to claim 4, wherein R_7 is halogen.

7. A pharmaceutical composition comprising a compound of formula (I) together with a pharmaceutically acceptable carrier.

8. A method of hormonal therapy, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of formula (I).

9. A method for the treatment or prevention of androgen receptor dependent conditions, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of formula (I).

10. A method according to claim 8 or 9, comprising administering a therapeutically effective amount of a compound of formula (I) orally.

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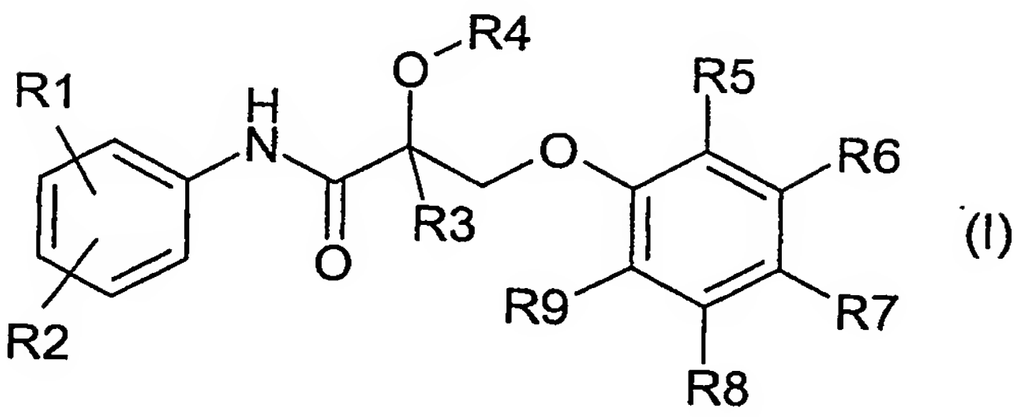
ABSTRACT

Compounds of formula (I)



(I)

wherein R_1 to R_9 are as defined and pharmaceutically acceptable salts and esters thereof, are disclosed. The compounds of formula (I) possess utility as tissue-selective androgen receptor modulators (SARM) and are useful in hormonal therapy, e.g. in the treatment or prevention of male hypogonadism and age-related conditions such as andropause.

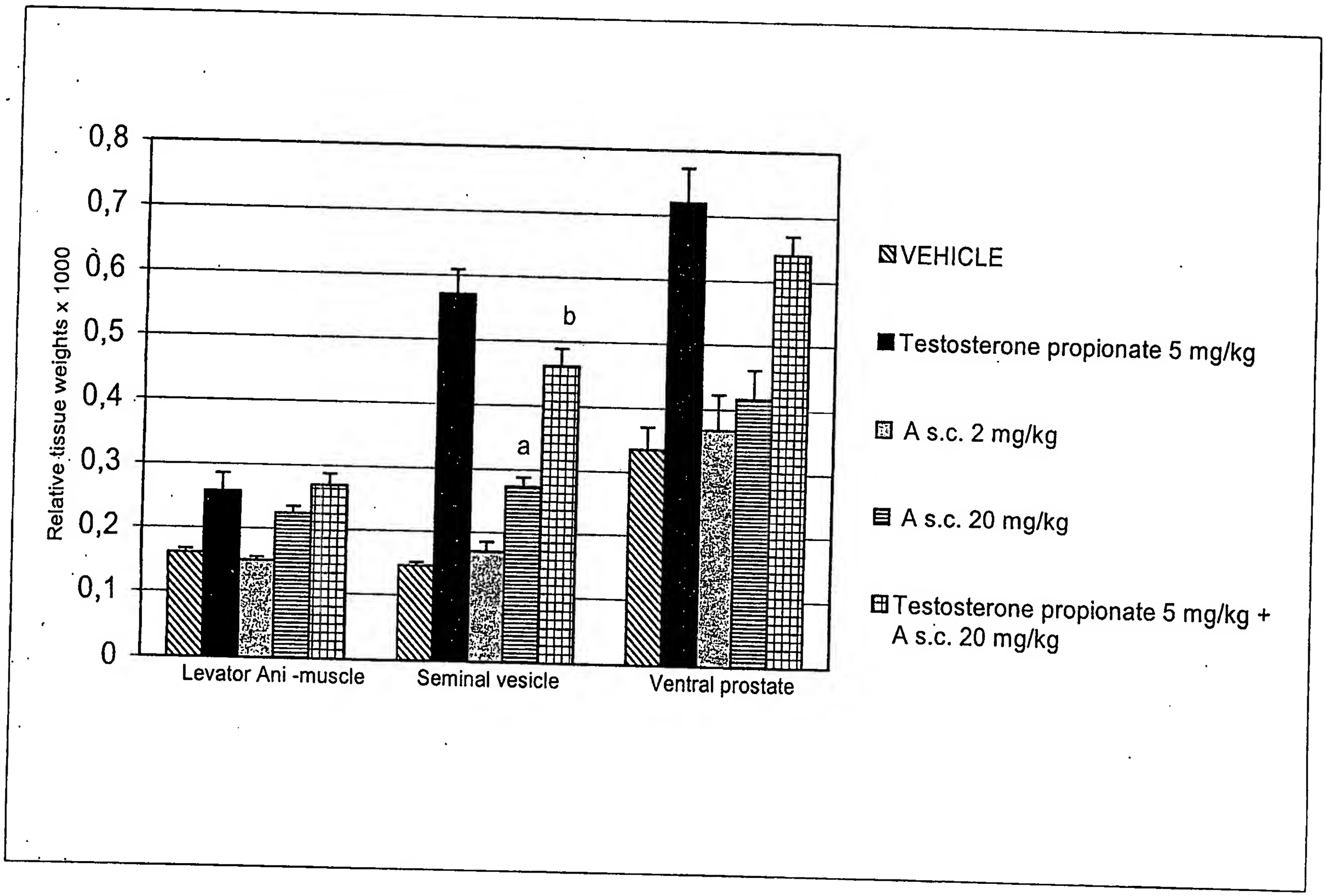

0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
Relative tissue weights x 1000
a
b
Levator Ani -muscle
Seminal vesicle
Ventral prostate
VEHICLE
Testosterone propionate 5 mg/kg
A s.c. 2 mg/kg
A s.c. 20 mg/kg
Testosterone propionate 5 mg/kg + A s.c. 20 mg/kg

FIG. 1